IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

NATERA, INC.,	)	
	)	
Plaintiff,	)	
	)	
v.	)	C.A. No. _____
	)	
ARCHERDX, INC.,	)	**JURY TRIAL DEMANDED**
	)	
Defendant.	)	

COMPLAINT FOR PATENT INFRINGEMENT

Plaintiff Natera, Inc. ("Natera"), for its Complaint against defendant ArcherDX, Inc. ("Archer"), hereby alleges as follows:

OVERVIEW OF THE ACTION

1. This is a patent infringement action brought under 35 U.S.C. § 271 arising from Archer's infringement of Natera's United States Patent No. 10,538,814 ("the '814 patent") by the manufacture, use, sale, and offer to sell of Archer's LiquidPlex (previously called Reveal ctDNA), Stratafide, and Personalized Cancer Monitoring ("PCM") products (collectively, the "Accused Products"), all of which use Archer's Anchored Multiplex PCR ("AMP") on cell free DNA. ArcherDX does not have freedom to operate its AMP products for minimal residual disease ("MRD") and personalized cancer monitoring. Natera brings this action to stop Archer's infringement of Natera's innovative, patented technology.

THE PARTIES

2. Plaintiff Natera is a corporation organized and existing under the laws of the state of Delaware, with its principal place of business at 201 Industrial Road, San Carlos, California 94070.

3. Founded in 2004, Natera (f.k.a. Gene Security Network) is a pioneering molecular technology company with industry-leading healthcare diagnostics products. Natera is dedicated to improving disease management for oncology, reproductive health, and organ transplantation. For well over a decade, Natera has been researching and developing non-invasive methods for analyzing DNA in order to help patients and doctors manage diseases. These ongoing efforts have given rise to a number of novel and proprietary genetic testing services to assist with life-saving health management.

4. Since 2009, Natera has launched ten molecular tests, many of which are available through major health plans accounting for more than 140 million covered persons in the United States. Natera's own robust laboratory processes thousands of genetic tests per month.

5. Natera's pioneering and ongoing innovation is especially evident in the area of cell-free DNA ("cfDNA")-based testing. In the cfDNA field, Natera has developed unique and highly optimized cfDNA-based processes that can be used to test non-invasively for a range of conditions. Natera developed an industry-leading cfDNA test, Panorama, which showcases Natera's mastery of cfDNA in the field of non-invasive diagnostics. Natera is considered the industry leading test in this space, with over two million tests performed commercially, and with more than twenty-six peer-reviewed publications. Natera has also applied its cfDNA platform to the challenge of detecting and monitoring cancer.

6. In detecting and monitoring cancer, the use of minimally invasive, blood-based tests offers significant advantages over older methods, such as invasive tumor biopsy. But the significant technological challenge is that such blood-based testing requires the measurement of very small amounts of relevant genetic material—circulating-tumor DNA ("ctDNA")—within a much larger blood sample. Natera's approach combines proprietary molecular biology and

computational techniques to measure genomic variations in tiny amounts of DNA, representing a fundamental advance in molecular biology.

7. Natera has researched and developed cfDNA technology to provide patients and healthcare providers with tools for early, clinically meaningful detection and monitoring of cancer.

8. Natera's cfDNA platform is the product of well over a decade of hard work and investment of, on average, more than fifty million dollars per year in research and development. Natera has expended substantial resources researching and developing its technologies and establishing its reputation among physicians, insurers, and regulators as a company committed to sound science and consistently accurate, reliable results. This research, and the technological innovations resulting therefrom, are protected by a substantial patent portfolio, with over 200 patents issued or pending worldwide, including greater than 60 in the field of oncology.

9. Among these patented inventions is the '814 patent, which Archer infringes. Archer has used Natera's patented cfDNA technology without permission and in violation of the patent laws.

10. Defendant Archer is a corporation organized and existing under the laws of the state of Delaware, having a principal place of business at 2477 55th Street, Suite 202, Boulder, CO 80301.

11. Instead of developing its own science for its cancer detection and monitoring products, Archer has unlawfully used Natera's patented technology.

JURISDICTION AND VENUE

12. This is an action for patent infringement arising under the Patent Laws of the United States, 35 U.S.C. § 1, *et seq*. This Court has jurisdiction under 28 U.S.C. §§ 1331 and

1338(a) because this is a civil action arising under the Patent Act and declaratory judgment jurisdiction under 28 U.S.C. §§ 2201-2202.

13. This Court has personal jurisdiction over Archer because Archer is a Delaware corporation.

14. This Court also has jurisdiction over Archer because, upon information and belief, Archer, directly or indirectly, uses, offers for sale, and/or sells the Accused Products throughout the United States, including in this judicial district.

15. This Court also has jurisdiction over Archer because Archer has availed itself of this forum, initiating civil actions in this jurisdiction including *ArcherDX, Inc. et al v. QIAGEN Sciences, LLC et al*, 18-1019-MN (D. Del. 2018).

16. Venue is proper in this Court under 28 U.S.C. § 1400(b) because Archer is a Delaware corporation.

BACKGROUND

17. Since 2004, Natera has been a global leader in genetic testing, diagnostics, and DNA testing, including cfDNA testing. Natera's mission is to improve the management of disease worldwide and focuses on reproductive health, oncology, and organ transplantation. In pursuit of these goals, Natera has developed novel technologies to make significant and accurate clinical assessments from the miniscule amounts of cfDNA present in a single blood sample. These technologies include methods to manipulate cfDNA in unconventional ways in order to capture information about genetic variations in cfDNA and usefully transform that information for noninvasive testing.

18. Natera develops and commercializes innovative, non-traditional methods for manipulating and analyzing cfDNA, and offers a host of proprietary cfDNA genetic testing services to the public to assist patients and doctors to evaluate and track critical health concerns.

19. Since its founding, Natera has researched, developed, and released ten molecular tests with applications in prenatal diagnostics, cancer, and organ transplants, many of which are available through major health plans, or covered by Medicare or Medicaid, and therefore available to most patients in need of those tests. Natera's tests have helped more than two million people to date. Natera's robust laboratory now processes tens of thousands of tests per month in the United States and internationally, improving the ability of physicians to monitor and manage crucial health issues and patients to prosper around the world.

20. Building on these innovations, in 2017, Natera launched its cfDNA diagnostic test to detect and monitor cancer, called Signatera®. Signatera® is a personalized ctDNA surveillance tool that detects MRD when assessing disease recurrence or treatment response in solid tumors. Signatera® is designed to screen for multiple tumor-derived targets with each assay. It is optimized to detect extremely low quantities of ctDNA and provides early knowledge of disease recurrence with a >99.5% clinical test specificity.

21. MRD assessment has become a standard of care in the management of patients with hematological malignancies, but until recently it has not been possible in solid cancers due to technical limitations. Accurate MRD testing and molecular monitoring offers the potential for physicians to change or escalate treatment in patients who are MRD-positive, and to de-escalate or avoid unnecessary treatment in patients who are MRD-negative. It also holds potential as a surrogate endpoint in clinical trials.

22. Natera's technology has been validated in multiple clinical studies. In Cancer Research UK/University College London's Tracking Cancer Evolution through Therapy ("TRACERx"), Natera's technology was used for the multi-year monitoring of patient-specific single-nucleotide variants (SNVs) in plasma, to understand the evolution of cancer mutations

over time, and to monitor patients for disease recurrence. Results from the first 100 early-stage lung cancer patients analyzed as part of the study were featured on the cover of the May 2017 issue of Nature and showed that an early prototype version of Signatera identified 43% more ctDNA-positive early-stage lung cancer cases than a generic lung cancer panel and demonstrated its potential to detect residual disease, measure treatment response, and identify recurrence up to 11 months earlier than the standard of care, with a sensitivity of 93% at time of relapse.

23. Natera has also collaborated with Aarhus University in Denmark, Imperial College London, University of Leicester, Institute Jules Bordet, Fox Chase Cancer Center, University of California, San Francisco, and Foundation Medicine, Inc with respect to cancer research.

24. The U.S. Food and Drug Administration ("FDA") recognized the importance of Natera's Signatera® and granted it "Breakthrough Device" designation on May 6, 2019. That designation will help accelerate FDA assessment and review of Signatera as an in vitro diagnostic for use in pharmaceutical trials.

25. Signatera's validation has also led Medicare to issue a draft Local Coverage Determination ("LCD") for Signatera in March 2019. In its draft LCD, Medicare determined that "[t]he analytical validity and clinical validity of minimal residual disease testing using cell-free DNA, and Signatera in particular, appears to be well established based on available information for the test."

26. The '814 patent resulted from Natera's years-long research in developing innovative new methods for amplifying and sequencing cell-free DNA.

General Background of the Invention

27. The ’814 patent, attached hereto as Exhibit 1, is entitled “Methods for Simultaneous Amplification of Target Loci” and was issued by the United States Patent and Trademark Office (“USPTO”) on January 21, 2020. Natera owns the ’814 patent, including the right to enforce it and seek damages for infringement.

28. The ’814 patent claims methods for simultaneously amplifying multiple nucleic acid regions of interest in a single reaction volume. The claimed methods use polymerase chain reaction (“PCR”) to amplify and high-throughput sequencing (“HTS”) to sequence the nucleic acids. Independent claim 1 of the ’814 patent recites:

> A method for amplifying and sequencing DNA, comprising:
>
> ligating adaptors to cell-free DNA isolated from a biological sample, wherein the adaptors each comprises a universal priming site;
>
> performing a first PCR to simultaneously amplify at least 10 target loci using a universal primer and at least 10 target-specific primers in a single reaction volume;
>
> performing a second, nested PCR to simultaneously amplify the at least 10 target loci using the universal primer and at least 10 inner target-specific primers in a single reaction volume, wherein at least one of the primers comprises a sequencing tag;
>
> performing high-throughput sequencing to sequence the amplified DNA comprising the target loci.

The ’814 Patent Is Not Directed To A Natural Phenomenon And Its Steps Were Not Routine Or Conventional

29. The claims of the ’814 patent are not directed to a natural law or natural phenomenon. Rather, they are directed to amplifying and sequencing DNA in a sample using synthetic primers and amplification products to provide a novel and innovative solution to problems peculiar to the particular problem of amplifying and sequencing small amounts of cell-free DNA from tumor cells in a biological sample.

30. The ’814 patent claims are directed to specific, unconventional, non-routine methods for overcoming previously unresolved problems in this area. For example, as of the date of the invention, it would not have been routine or conventional to amplify and use HTS to sequence nucleic acids obtained from circulating tumor DNA with the use of a universal primer and a sequencing tag in the context of the invention.

31. In allowing ’814 patent claims, the USPTO examiner found the claims to be non-routine and non-conventional, and stated:

> [T]he claims have been carefully reviewed and the claimed invention distinguishes over the art because the closest references in the art do not teach, or render obvious, each aspect of the claimed invention. The closest art, Chowdary et al. (US PgPub 20080305473; December 2008) teaches a method of nested multiplex amplification of circulating tumor cells, but there are significant differences between the teachings of Chowdary and the claimed method steps. Chowdary focuses on amplification of nucleic acids obtained from circulating tumor cells and not on circulating nucleic acids, Chowdary does not teach any sequencing steps, does not incorporate a universal or common primer and does not include a sequencing tag. Further, Chowdary specifically teaches away from modification to focus on circulating nucleic acids, Chowdary specifically includes a step of isolation of circulating tumor cells (CTCs) followed by extraction of nucleic acids and amplification of the nucleic acid, steps which would exclude modifying Chowdary to arrive at the method steps as claimed.
>
> Further, an additional reference, Gocke et al. (US Patent 6156504; December 2000) teaches analysis of circulating nucleic acids that include semi-nested amplification, and a general mention of multiplex amplification. However, there are also significant differences between Gocke and the claimed method steps because Gocke only mentions sequencing in a prophetic example, does not teach or suggest the inclusion of universal or common primers or the inclusion of sequencing tags.
>
> Therefore, since neither Chowdary nor Gocke teach or suggest each and every step of the method, as claimed, the claims are novel and non-obvious over the prior art.

ARCHER'S INFRINGING ACTIVITIES

32. Archer sells products using its AMP technology on cell-free tumor DNA. One such product is LiquidPlex, which applies AMP to ctDNA to detect and monitor genes commonly associated with cancers. Another such product is Stratafide, which is a pan-solid tumor test designed to identify actionable genomic alterations in tissue or blood samples. A third such product is PCM, a bespoke product that uses AMP for cancer treatment monitoring and recurrence surveillance.

33. Attached as Exhibit 2 is a preliminary and exemplary claim chart describing Archer's infringement of claim 1 of the '814 patent. Exhibits 3-11 are supporting documents for the Exhibit 2 chart. The claim chart is not intended to limit Natera's right to modify the chart or allege that other activities of Archer infringe the identified claim or any other claims of the '814 patent or any other patents. Archer infringes more than one claim of the '814 patent.

34. Exhibit 2 is hereby incorporated by reference in its entirety. Each claim element in Exhibit 2 that is mapped to Archer's Accused Products shall be considered an allegation within the meaning of the Federal Rules of Civil Procedure and therefore a response to each claim element is required.

35. Archer's AMP process is used in its LiquidPlex product.

36. Archer's AMP process is used in its Stratafide product.

37. Archer's AMP process is used in its PCM product.

38. Archer's AMP process is a method for amplifying and sequencing DNA.

39. Archer's AMP process, as used in the LiquidPlex, Stratafide, and PCM products, includes ligation of adaptors to cell-free DNA isolated from a biological sample.

40. Archer's AMP process includes ligation of adaptors that each comprise a universal priming site.

41. Archer's AMP process, as used in the LiquidPlex, Stratafide, and PCM products, includes a first PCR to simultaneously amplify at least 10 target loci using a universal primer and at least 10 target-specific primers in a single reaction volume.

42. Archer's AMP process, as used in the LiquidPlex, Stratafide, and PCM products, includes a second, nested PCR to simultaneously amplify the at least 10 target loci using the universal primer and at least 10 inner target-specific primers in a single reaction volume.

43. Archer's AMP process includes primers comprising a sequencing tag.

44. Archer's AMP process includes performing HTS to sequence the amplified DNA comprising the target loci.

45. Archer's AMP process, as used in the LiquidPlex, Stratafide, and PCM products, is performed on a biological sample that is a blood, plasma, serum, or urine sample.

46. Archer's AMP process includes subjecting the isolated cell-free DNA to blunting ending, dA-tailing, and adaptor ligation.

47. Archer's AMP process uses an adaptor that includes a molecular barcode.

48. In Archer's AMP process, the second PCR is one-sided nested PCR.

49. Archer's AMP process includes multiplex sequencing of amplified DNA of multiple samples in a single sequencing lane.

50. Archer's AMP process, as used in the LiquidPlex, Stratafide, and PCM products, includes a first PCR that simultaneously amplifies at least 50 target loci using the universal primer and at least 50 target-specific primers in a single reaction volume.

51. Archer's AMP process, as used in the LiquidPlex, Stratafide, and PCM products, includes a first PCR that simultaneously amplifies at least 100 target loci using the universal primer and at least 100 target-specific primers in a single reaction volume.

52. Archer's AMP process, as used in the LiquidPlex, Stratafide, and PCM products, includes a second PCR that simultaneously amplifies at least 50 target loci using the universal primer and at least 50 target-specific primers in a single reaction volume.

53. Archer's AMP process, as used in the LiquidPlex, Stratafide, and PCM products, includes a second PCR that simultaneously amplifies at least 100 target loci using the universal primer and at least 100 target-specific primers in a single reaction volume.

54. In Archer's AMP process, as used in the LiquidPlex, Stratafide, and PCM products, the isolated cell-free DNA are tagged with up to 1024 different molecular barcodes.

55. In Archer's AMP process, as used in the LiquidPlex, Stratafide, and PCM products, the isolated cell-free DNA are tagged with 1024-65536 different molecular barcodes.

56. In Archer's AMP process, as used in the LiquidPlex, Stratafide, and PCM products, the concentration of each target-specific primer of the first and/or second PCR is less than 20 nM.

57. In Archer's AMP process, as used in the LiquidPlex, Stratafide, and PCM products, the concentration of each target-specific primer of the first and/or second PCR is less than 10 nM.

58. In Archer's AMP process, as used in the LiquidPlex, Stratafide, and PCM products, the length of the annealing step of the first and/or second PCR is at least 3 minutes.

59. In Archer's AMP process, as used in the LiquidPlex, Stratafide, and PCM products, the length of the annealing step of the first and/or second PCR is at least 5 minutes.

60. In Archer's AMP process, as used in the LiquidPlex, Stratafide, and PCM products, at least 90% of the amplified DNA map to the target loci.

61. In Archer's AMP process, as used in the LiquidPlex, Stratafide, and PCM products, target loci include SNP loci.

62. In Archer's AMP process, as used in the LiquidPlex, Stratafide, and PCM products, the cell-free DNA comprises DNA from mixed origin.

63. In Archer's AMP process, as used in the LiquidPlex, Stratafide, and PCM products, the cell-free DNA comprises DNA from a tumor.

64. Archer began selling and offering to sell LiquidPlex on or about September 22, 2016.

65. Archer received the FDA's Breakthrough Device Designation for LiquidPlex in or about January 2019, and Archer intends to sell the product for non-research purposes immediately upon approval.

66. Archer received the FDA's Breakthrough Device Designation for Stratafide on or about January 2019, and Archer intends to sell the product immediately upon approval.

67. Archer received the FDA's Breakthrough Device Designation for PCM on or about January 15, 2020, and Archer intends to sell the product immediately upon approval.

68. Archer has its own CLIA-certified laboratory that has or will use the Accused Products.

69. LiquidPlex is sold as a kit or as component parts so that the assay can be performed by others.

70. Stratafide will be sold as a kit or as component parts so that the assay can be performed by others.

71. PCM will be sold as a kit or as component parts so that the assay can be performed by others.

72. Archer's development of its Accused Products has been aided by access to and use of Natera's innovative research and development.

73. For example, Natera worked with Dr. Charles Swanton at the University College London ("UCL") to validate its Signatera® technology in the TRACERx lung cancer study. Subsequent to that collaboration, Archer announced that it was collaborating with Dr. Swanton on that same study. A January 14, 2020 Archer press release states that Archer has an "on-going collaboration" with Dr. Swanton, who is now "utilizing ArcherDX's technology … to help achieve" the goals of the TRACERx study.

74. Upon information and belief, Archer was able to develop its Accused Products, including its Stratafide and PCM products, as a direct result of unlawful use of Natera's innovative technology.

75. Archer is a direct competitor of Natera in the market for recurrence monitoring for lung cancer.

76. Archer has knowledge of the '814 patent at least as early as the date of this complaint.

COUNT I
(Infringement of U.S. Patent No. 10,538,814)

77. Natera repeats and realleges the foregoing paragraphs as if fully set forth herein.

78. Natera is the owner of the '814 patent, which was duly and legally issued by the USPTO on January 21, 2020.

79. Archer has infringed and continues to infringe at least one claim of the '814 patent pursuant to 35 U.S.C. § 271(a), literally or under the doctrine of equivalents, by making,

using, offer to sell, or selling within the United States, or importing into the United States, the Accused Products without authority.

80. Archer has infringed and continues to infringe at least one claim of the ’814 patent pursuant to 35 U.S.C. § 271(b), literally or under the doctrine of equivalents, by inducing others through instructional materials, product manuals, and technical materials, disseminating promotional/marketing materials that describe the workflows and use of those tests, or otherwise instructing others to use the Accused Products, or components thereof, in a manner that infringes at least claim of the ’814 patent. At least as of the date hereof, Archer makes, sells and distributes the Accused Products, or components thereof, with the knowledge that these instructions will cause others to infringe at least one claim of the ’814 patent, and therefore Archer induces others to perform activities that directly infringe at least one claim of the ’814 patent.

81. Archer has infringed and continues to infringe at least one claim of the ’814 patent pursuant to 35 U.S.C. § 271(c), literally or under the doctrine of equivalents, by distributing, offering to sell or selling the Accused Products, or components thereof, within the United States for use by others to practice at least one of the claimed methods of the ’814 patent. The Accused Products each constitute a material part of the invention of the ’814 Patent, and, at least as of the date hereof, Archer knows the Accused Products, and components thereof, to be especially made or especially adapted for use in a manner that infringes the ’814 patent. Furthermore, none of the Accused Products is a staple article or commodity of commerce suitable for substantial noninfringing use. Archer sells and offers for sale the Accused Products, or components thereof, with the knowledge that its instructions and workflows will cause others to perform activities that directly infringes at least one claim of the ’814 patent.

82. Archer's infringement has damaged and will continue to damage Natera, which is entitled to recover the damages resulting from Archer's wrongful acts in an amount to be determined at trial, and in any event no less than a reasonable royalty.

83. Moreover, Archer's infringement has caused, and will continue to cause, irreparable injury to Natera, for which damages are an inadequate remedy, unless Archer is enjoined from any and all activities that would infringe the claims of the '814 patent.

COUNT II
(Declaratory Judgment of Infringement of U.S. Patent No. 10,538,814)

84. Natera repeats and realleges the foregoing paragraphs as if fully set forth herein.

85. Archer has sought and received the FDA's Breakthrough Device designation for the Accused Products. Natera believes, and on that basis alleges, that Archer intends to engage in the commercial manufacture, use, offer for sale, and sale of the Accused Products if and when it receives FDA approval to do so.

86. An actual, substantial, and justiciable controversy has arisen and now exists between the parties concerning whether, *inter alia*, the manufacture, use, offer for sale, sale, and/or importation of the Accused Products has or will infringe one or more claims of the '814 patent.

87. Natera is entitled to a judicial declaration that Archer has infringed or will infringe, directly and/or indirectly, literally and/or under the doctrine of equivalents, one or more claims of the '814 patent.

88. Archer's infringement has damaged and will continue to damage Natera, which is entitled to recover the damages resulting from Archer's wrongful acts in an amount to be determined at trial, and in any event no less than a reasonable royalty.

89. Moreover, Archer's infringement has caused, and will continue to cause, irreparable injury to Natera, for which damages are an inadequate remedy, unless Archer is enjoined from any and all activities that would infringe the claims of the '814 patent.

PRAYER FOR RELIEF

WHEREFORE, Natera prays for a judgment in its favor and against Archer and respectfully request the following relief:

A. A judgment that Archer directly infringes, induces infringement, and contributorily infringes the '814 patent;

B. An order enjoining Archer and its officers, directors, agents, servants, affiliates, employees, divisions, branches, subsidiaries, parents, and all others acting in active concert therewith from further infringement of the '814 patent;

C. Damages or other monetary relief, including, but not limited to, costs and pre and post-judgment interest, to Natera;

D. A determination that this is an exceptional case under 35 U.S.C. § 285 and an award of attorneys' fees and costs to Natera in this action;

E. Costs and expenses in this action;

F. An order awarding Natera any such other relief as the Court may deem just and proper under the circumstances.

JURY DEMAND

Pursuant to Rule 38(b) of the Federal Rules of Civil Procedure, Natera hereby demands a jury trial as to all issues so triable.

MORRIS, NICHOLS, ARSHT & TUNNELL LLP

/s/ Jack B. Blumenfeld

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